

LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Chemotherapy and Immunotherapy in Early-Stage NSCLC: Neoadjuvant vs Adjuvant Therapy



Heather Wakelee, MD
Professor of Medicine
Stanford University Medical Center
Stanford, California

H&O Which patients with early-stage non-small cell lung cancer (NSCLC) are eligible for surgical resection?

HW We perform surgical resection in nearly all patients with stage I or II NSCLC unless surgery is contraindicated for medical reasons. The uncertainty comes in with stage III NSCLC. Many physicians will recommend surgery in patients who have stage III NSCLC based on tumor invasion or having 1 or 2 positive lymph nodes. A multidisciplinary tumor board (MTB) discussion is a good idea for all stage III patients but is especially important when deciding on surgery in a patient who has stage III NSCLC with multiple positive lymph nodes.

H&O Is chemotherapy recommended for all patients who undergo surgical resection?

HW Chemotherapy is recommended for all stage III patients and any stage II patients with lymph node involvement. There is a division regarding the patients with stage I disease, with chemotherapy recommended in stage IB but not in stage IA. The controversy comes in because the definition of stage IB has evolved. Now, with the eighth edition of the tumor, node, metastasis (TNM) classification, many of the larger tumors that were formerly classified as stage IB tumors are classified as stage II.

H&O How do physicians decide between neoadjuvant and adjuvant chemotherapy?

HW The trials of adjuvant and neoadjuvant chemotherapy date back close to 20 years. The adjuvant trials finished first, so most of the neoadjuvant trials were halted before they produced definitive answers. Although adjuvant chemotherapy was considered the gold standard in the chemotherapy-only era because of the history of the trials, experts generally feel that the benefit of chemotherapy is similar whether it is given before or after surgery. We consider neoadjuvant chemotherapy for some patients with stage III NSCLC because we have a bit more data on this approach in stage III. We are less likely to use neoadjuvant chemotherapy in stage II NSCLC, but sometimes we use this approach to shrink the tumor before surgery if the tumor is in a tricky location.

H&O How has the introduction of immunotherapy changed this approach?

HW The introduction of immunotherapy has completely altered this approach. Chemotherapy is effective in most patients with NSCLC, regardless of the tumor histology. However, with the introduction of immunotherapy, we do additional tumor testing to detect any underlying driver mutations, such as those in the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase

(*ALK*). Adjuvant osimertinib (Tagrisso, AstraZeneca) is an option for patients with tumors with *EGFR* mutations. A recent trial called ALINA produced positive results with the adjuvant use of alectinib (Alecensa, Genentech) for patients with *ALK* tumor mutations. Perioperative immunotherapy is unlikely to work in patients with certain driver mutations. It is important that we do the testing so that patients with *EGFR*- and *ALK*-mutated tumors get the appropriate targeted therapy and everyone else is considered for immune-based therapy, if appropriate.³ We also look at the level of programmed death ligand 1 (PD-L1) protein on a tumor, which is an imperfect but helpful biomarker for response to immunotherapy; higher levels indicate a higher chance of response to immune therapy.

The phase 3 CheckMate 816 trial, which looked at the use of neoadjuvant immunotherapy with nivolumab (Opdivo, Bristol Myers Squibb) plus chemotherapy, showed a profound effect on event-free survival (EFS) in patients with stage IB to IIIA resectable NSCLC.⁴ EFS refers to disease-free survival (DFS) plus any event that keeps the patient from getting surgery, such as extensive cancer growth. This trial used the older cutoff of greater than 4 cm for stage IB, but tumors that large would now be considered stage IIA. Since the CheckMate 816 trial, 2 trials of adjuvant therapy have shown improvements in DFS. DFS is a different endpoint than EFS, which was used in the neoadjuvant trial. DFS is also different from any trial that involves patients enrolled before surgery because it includes events that prevented the surgery from taking place. Another difference is that the neoadjuvant trial used concurrent chemotherapy and immunotherapy, whereas the adjuvant trials gave sequential chemotherapy and immunotherapy. Trials of adjuvant therapy have slightly different populations than trials of neoadjuvant therapy because patients have already had surgery vs being theoretically able to undergo surgery. We have seen that immunotherapy and chemotherapy are additive in the metastatic setting, so it is not surprising that they were additive in earlier stages of lung cancer. The hazard ratios (HRs) for improvements in all these studies were in the range of 0.6 to 0.7.

Based on these studies, what is the best course of action? There is a theoretical advantage to starting systemic treatment right away and getting immunotherapy into the body while antigen levels are high because there is still a tumor present before the surgery. On the other hand, the idea of surgery right away is appealing because some patients and surgeons want to get the tumor out as soon as possible. If surgery is postponed, there is a risk of losing the opportunity for it. In studies of neoadjuvant therapy, approximately 20% of patients do not make it to surgery—although these trial participants may not be representative of the general NSCLC population, so the

true number is likely a bit lower. When we look at survival outcomes for the 2 approaches, they are not so far apart that there is a clear winner. We did see a head-to-head trial of neoadjuvant vs adjuvant treatment in melanoma, in which neoadjuvant treatment was more effective, which suggested that the same might be true in NSCLC.

Until earlier this year, the decision was between pure neoadjuvant and pure adjuvant therapy. If a patient had already had surgery, we knew that we could use adjuvant therapy with atezolizumab (Tecentriq, Genentech), based on the IMpower010 study,⁵ or pembrolizumab (Keytruda, Merck), based on the PEARLS/KEYNOTE-091 trial.⁶ Atezolizumab has been shown to work especially well in patients with high PD-L1 levels on their tumor. We now have results from four phase 3 trials that combined neoadjuvant and adjuvant immunotherapy: AEGEAN, NEOTORCH, KEYNOTE-671, and CheckMate 77T.⁷⁻¹²

For most patients,
we use a combination
of chemotherapy
and immunotherapy
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In the AEGEAN trial, 802 patients with resectable stage II or IIIB (N2 stage) NSCLC were randomized in a 1:1 ratio to receive neoadjuvant durvalumab (Imfinzi, AstraZeneca) or placebo plus platinum-based chemotherapy, followed by adjuvant durvalumab or placebo. In results that Dr John Heymach presented at the American Association for Cancer Research Annual Meeting 2023 and recently published in the *New England Journal of Medicine*, the addition of perioperative durvalumab to treatment improved EFS (HR, 0.68) and pathological complete response.^{7,8}

In the NEOTORCH trial, patients with stage II or III NSCLC were randomized in a 1:1 ratio to receive toripalimab or placebo plus chemotherapy for 3 cycles before surgery and 1 cycle after surgery, followed by toripalimab or placebo monotherapy for up to 1 year. In results among 404 patients with stage III disease that Dr Shun Lu presented at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting, patients in the toripalimab group had better EFS than those in the placebo group, with an HR of 0.40.⁹

In the KEYNOTE-671 trial, 797 patients with resectable stage II, IIIA, or IIIB (N2 stage) NSCLC were assigned in a 1:1 ratio to neoadjuvant pembrolizumab or placebo plus cisplatin-based chemotherapy, followed by surgery and adjuvant pembrolizumab or placebo. In results that we presented at the 2023 ASCO Annual Meeting and published in the *New England Journal of Medicine*, the pembrolizumab group had better EFS (HR, 0.58), major pathological response, and pathological complete response than the placebo group.¹⁰ At an update at the European Society for Medical Oncology (ESMO) Congress 2023, the trial reached a statistically significant overall survival (OS) benefit,¹¹ and the regimen now has US Food and Drug Administration (FDA) approval.

Finally, interim results from the phase 3 CheckMate 77T trial that were presented at the ESMO Congress 2023 showed that neoadjuvant nivolumab plus chemotherapy followed by adjuvant nivolumab significantly improved median EFS compared with chemotherapy plus adjuvant placebo, with an HR of 0.58. We are seeing frequent updates from the other trials as well, so the field is evolving rapidly.¹²

The improvement in EFS was impressive in all 4 trials. The NEOTORCH results are different from the results of the other studies because NEOTORCH has only reported data on stage III patients, who are at increased risk for recurrence and therefore are probably more likely to benefit from immunotherapy. This study also excluded patients with tumors with *EGFR* mutations. Because this was an Asian study, excluding the patients with *EGFR*-mutated tumors ended up excluding many patients with adenocarcinoma, so nearly all patients had squamous cell carcinoma rather than adenocarcinoma. Excluding patients with *EGFR* mutations also wound up making most of the participants men because of the high prevalence of *EGFR* mutations in lung cancer among women in Asia. It is difficult to know whether these results represent differences in the efficacy of the treatment regimens or among the study's population. In addition, it is difficult to know whether these results represent a difference from the results of CheckMate 816, the original study of pure neoadjuvant treatment, in which the HR for EFS (disease progression, disease recurrence, or death) was 0.63. So how do we choose among these 4 regimens based on these 4 trials, all of which produced very good EFS? Is it worth giving patients an extra year of treatment if there are good results with neoadjuvant treatment alone? We have not yet conducted the trial to address these questions.

We also saw interesting preliminary results from the RATIONALE-315 trial that were presented at the ESMO Congress 2023. This study showed improvements

in major pathological response and pathological complete response with the use of neoadjuvant and adjuvant tislelizumab vs placebo in patients with resectable stage II to IIIA NSCLC. EFS results are not yet available for this study.¹³

As noted, KEYNOTE-671 has just reached its OS endpoint and we suspect that the other trials will also hit their OS endpoint eventually, but in the meantime, do we all switch to a perioperative approach? Are there patients where a pure adjuvant or pure neoadjuvant approach makes sense?

H&O What approach do you use in your practice?

HW The approach depends on the patient. For my most recent patient with stage II NSCLC, we debated whether to go straight to surgery or not. It turned out that the patient's tumor PD-L1 level was 95%, which is very high, so there was a high probability of responding to immunotherapy. Their scan also had some concerning findings that were potentially suspicious for cancer in other areas but were not clear. I ended up recommending the CheckMate 816 approach of pure neoadjuvant treatment because I felt that the patient's probability of response was so high that they might be able to avoid additional treatment after surgery. However, we will consider adding additional adjuvant therapy if their tumor response is not fantastic at the time of surgery. Now that the FDA approves perioperative therapy with pembrolizumab based on the new OS results of KEYNOTE-671, that will be another option to discuss with our patients. We should eventually be able to identify which patients with stage II disease are cured with surgery alone and do not need additional systemic treatment. However, at this point, the tests are not good enough to tell us that.

For my patients with stage III NSCLC, I always start with neoadjuvant treatment, unless they have a driver mutation such as *EGFR* or *ALK* in their tumor. I look forward to learning more about which of these patients might benefit from the addition of adjuvant treatment, based on factors such as the pathological complete response and the circulating tumor DNA. If patients are not going to benefit from treatment, we want to be able to withhold it. Every treatment has side effects, and immunotherapy can produce lifelong conditions such as thyroid dysfunction.

H&O How do oncologists decide among systemic regimens, whether that means chemotherapy alone, chemotherapy plus immunotherapy, single-agent immunotherapy, or dual-agent immunotherapy?

HW Single-agent chemotherapy is no longer the standard of care unless a patient has a targetable driver mutation where chemotherapy will be used before targeted therapy or a contraindication to immunotherapy, such as a severe underlying autoimmune disease or organ transplant. For most patients, we use a combination of chemotherapy and immunotherapy as neoadjuvant or perioperative treatment. Patients who receive pure adjuvant treatment receive sequential treatment with chemotherapy followed by immunotherapy after surgery.

Regarding the approach of immunotherapy without chemotherapy, we have few data. The PEARLS/KEYNOTE-091 trial had a subgroup of patients who did not receive chemotherapy for a variety of reasons and these patients did poorly, so we do not have data at this time to support the pure immunotherapy strategy. As for dual immunotherapy, the CheckMate 816 study had a small component using the combination of nivolumab/ipilimumab (Yervoy, Bristol Myers Squibb) that was presented at the ESMO Congress 2023.¹⁴ This trial had some intriguing findings but was too small to make any definitive conclusion. The combination had a worse EFS for about 9 months and then started to look better than chemotherapy with longer-term follow-up, so a combination of these agents and chemotherapy may be explored in the future, particularly in patients with tumors that do not have PD-L1 expression.

Disclosures

Dr Wakelee has received direct payment for serving on the Data and Safety Monitoring Committee of Mirati; has served as a noncompensated consultant to Genentech/Roche and Merck; and has received research funding (to institution) from Bayer, Arrys Therapeutics, AstraZeneca/MedImmune, Bristol Myers Squibb, Clovis Oncology, Genentech/Roche, Merck, Novartis, Seagen, Xcovery, and Helsinn.

Suggested Readings

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